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Proton transfer reactions of *N*-aryl triazolium salts: unusual *ortho*-substituent effects†

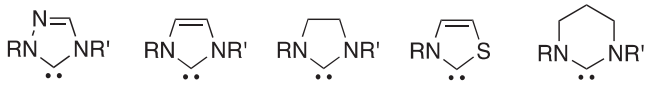
David E. Tucker[a], Peter Quinn[a], Richard S. Massey[a], Christopher J. Collett[b], David J. Jasiewicz[a], Christopher R. Bramley[a], Andrew D. Smith[b]** and AnnMarie C. O'Donoghue[a]*

Previous studies of the C(3)-hydrogen/deuterium exchange reactions of the triazolium ion conjugate acids of triazolyl N-heterocyclic carbenes revealed a change of mechanism under acidic conditions with N1-protonation to a dicationic salt. Interestingly, the data suggested an *increase* in pK_a^{N1} in the presence of a *N*-pentafluorophenyl substituent relative to other *N*-aryl substituents with hydrogens or methyl substituents rather than fluorines at the *ortho*-positions. To probe the presence of an apparent donor effect of a *N*-pentafluorophenyl substituent, which differs from the more common electron withdrawing effect of this group, we have studied the analogous deuterium exchange reactions of four triazolium salts with heteroatoms or heteroatom substituents in the 2-position and/or 6-position of the *N*-aryl ring. These include triazolium salts with *N*-2,4,6-tribromophenyl 11, *N*-2,6-dichlorophenyl 12, *N*-2-pyridyl 13 and *N*-2-pyrimidinyl 14 substituents. The log k_{ex} – p*D* profiles for 11, 12 and 14 were found to show similar trends at lower p*D*s as for the previously studied *N*-pentafluorophenyl triazolium salt, hence supporting the presence an apparent donor effect on pK_a^{N1}. Surprisingly, the log k_{ex} – p*D* profile for *N*-pyridyl salt 13 uniquely showed acid catalysis at lower p*D*s. We propose herein that this data is best explained by invoking an intramolecular general base role for the *N*-(2-pyridyl) substituent in conjunction with N1-protonation on the triazolium ring. Finally, the second order rate constants for deuteroxide ion catalysed C(3)-H/D exchange (k_{DO}, $M^{-1}\,s^{-1}$), which could be obtained from data at p*D*s >1.5, were used to provide estimates of C(3)-carbon acid pK_a^{C3} values for the four triazolium salts 11–14. © 2014 The Authors. Journal of Physical Organic Chemistry published by John Wiley & Sons Ltd.

Keywords: deuterium exchange; N-heterocyclic carbene; organic catalysis; proton transfer; triazolium

INTRODUCTION

Triazol-3-ylidenes **1** form a class of stable N-heterocyclic carbenes (NHC) that are frequently utilized as efficient, selective organic catalysts in a broad range of transformations.[1–7] Closely related to other stable NHCs including imidazole-2-ylidenes **2**, imidazolin-2-ylidenes **3**, thiazol-2-ylidenes **4** and trihydropyrimidin-2-ylidenes **5**, these carbenes have seen application in diverse areas of chemistry in addition to organic catalysis.[8–17] Common to most applications of NHCs of this type is the *in situ* generation of the carbene from the conjugate acid azolium salt precursor by use of an appropriate base. We and others have reported the kinetic acidities towards hydroxide ion and estimates of the aqueous pK_a values of the conjugate acid precursors to NHCs **1–5**.[18–23]



1 **2** **3** **4** **5**

In particular, we showed that the p*D* rate profiles for the deuterium exchange reactions of triazolium salt precursors **6** to triazol-3-ylidenes **7** reveal distinct differences from analogous data for NHCs **2–5**.[21] The presence of the additional ring nitrogen in triazolium ions **6** allows for alternative deuterium exchange mechanisms under more acidic conditions. Deuteronation at N(1) can occur to give dicationic triazolium ions **8**, which are precursors to monocationic NHCs **9**. At higher p*D* values, log k_{ex} values were observed to increase linearly with p*D* consistent with a first order dependence on deuteroxide ion and exchange *via* triazol-3-ylidenes **7** (path A, Scheme 1). At lower p*D* values, upward deviations were observed from the line of unit slope through the log k_{ex} – p*D* data consistent with a change in mechanism for deuterium exchange.

Of the large series of triazolium salts studied in aqueous solution, the altered dependence of log k_{ex} values on p*D* under more

* Correspondence to: AnnMarie C. O'Donoghue, Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK.
E-mail: annmarie.odonoghue@durham.ac.uk

** Correspondence to: Andrew D. Smith, EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife KY16 9ST, UK.
E-mail: ads10@st-andrews.ac.uk

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a D. E. Tucker, P. Quinn, R. S. Massey, D. J. Jasiewicz, C. R. Bramley, A. C. O'Donoghue
Department of Chemistry, Durham University, South Road, Durham DH1 3LE, UK

b C. J. Collett, A. D. Smith
EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife KY16 9ST, UK

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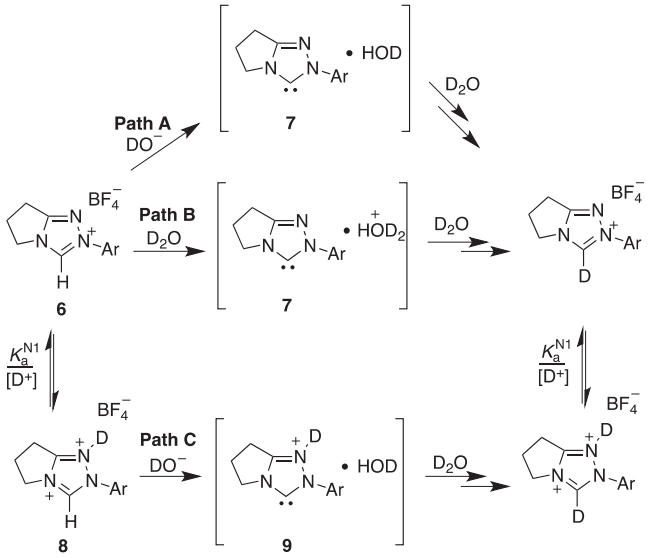
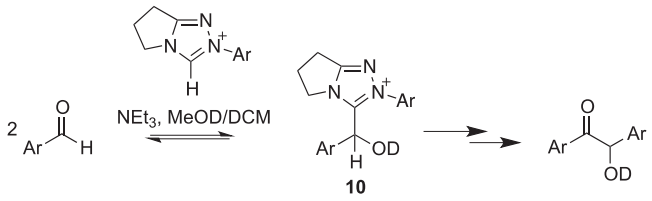


Scheme 1. Potential mechanistic pathways for deuterium exchange at C(3)-H of triazolium ions **6**

acidic conditions was most prevalent and occurred at significantly higher p*D* values, for *N*-pentafluorophenyl triazolium salt **6a** (Ar = C_6F_5).[21] For the structurally homologous series of triazolium salts **6**, the p*D* value for onset of the change in slope decreased in the order **6a** > **6b** > **6c** > **6d** ~ **6e** ~ **6f** (Ar = C_6F_5 (a); 4-CN-Ph (b); 4-F-Ph (c); Ph (d) [Correction added on 12 January 2015, after first online publication: H (d) was corrected to Ph (d)]; 2,4,6-(Me_3)-Ph (e); 4-MeO-Ph (f)). Only in the case of triazolium salt **6a** was the initial decreased dependence on p*D* further followed by a downward break at the lowest p*D*s studied. Data for **6a** could be fit by an equation describing either of two kinetically equivalent mechanistic options (path B or C, Scheme 1), which *both* require protonation at N1 of the triazolium ring. Path B involves a solvent promoted deuterium exchange reaction of the cationic triazolium salt **6a** with removal of active species *via* *N*-protonation to a dicationic triazolium ion **8a**. Path C entails no solvent reaction of the monocationic salt **6a** but instead the initial *N*-protonation at N(1) of salt **6a** followed by deuteroxide-catalysed exchange on the dicationic triazolium salt **8a**. Both of these mechanisms allow for the observed continued decrease in k_{ex}, the first order rate constants for deuterium exchange, with p*D*. On the basis of an analysis of the results of fitting through assumption of either pathway, we suggested that path C was the more likely option.

In order to explain the differences in the observed kinetic data for **6a** relative to **6b–f**, we postulated that the presence of an *ortho*-heteroatom, for example, fluorine, could favour protonation (or deuteronation) at N(1) resulting in an increased prevalence of dicationic triazolium salts **8** in the normal p*D* range and a higher pK_a (N1).[21] Of the substrates studied, only the *N*-pentafluorophenyltriazolium salt **6a** had *ortho*-heteroatoms rather than hydrogen or methyl groups on the *N*-aryl ring. A higher pK_a (N1) for salt **6a** seems counter-intuitive on the basis of the electron withdrawing, through-bond, inductive substituent effect of fluorine, which would be expected to decrease basicity at N(1). However, protonation at N(1) may be favoured in order to suppress unfavourable electrostatic interactions between this nitrogen and spacially proximal *N*-aryl *ortho*-fluorines, or, as a result of stabilizing through-space N^+-H…*ortho*-F interactions in the *N*-protonated salt.

In organocatalytic applications, varying the triazolium *N*-aryl substituent can have dramatic effects on yields and selectivities

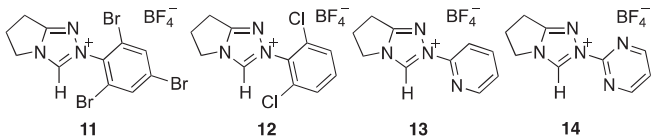


Scheme 2. Triazolium catalysis of the benzoin condensation

of typical triazolylidene-mediated transformations. In related mechanistic studies of triazolium catalysis of benzoin and Stetter reactions, we have also observed unexpected substituent effects in the presence of *ortho*-heteroatom substituents on the *N*-aryl ring of catalyst.[24] The common first step of both of these reactions involves the reaction of an aryl aldehyde and triazolium salt in the presence of base to give a deuteroxy aryl intermediate **10** (Scheme 2, shown for benzoin condensation). We have observed that *N*-aryl *ortho*-X-heteroatom substituents significantly increase rate and equilibrium constants for formation of adducts **10** relative to *para*-substituted and *ortho*-alkyl analogues. One possible explanation of these observations is the presence of an O-D…X interaction in the adduct similar to the N^+-H…*ortho*-F interaction proposed earlier.

In order to further probe these *ortho*-substituent effects, we have studied the deuterium exchange reactions of a number of additional triazolium salts **11–14** with heteroatoms or heteroatom substituents in the 2-position and/or 6-position of the *N*-aryl ring. The study of alternative triazolium salts with different *ortho*-halo substituents on the *N*-aryl ring was a logical next step. *Ortho*-Bromo and chloro-substituted substrates **11** and **12** were chosen for initial study because of the straightforward access to the relevant precursor *N*-aryl hydrazines required for their synthesis. *N*-2-Pyridyl and 2,6-pyrimidinyl salts **13** and **14** allow *ortho*-nitrogen atom substituent effects to be probed.

The data for these substrates also provides further evidence that path C, and not path B, is accountable for the altered dependence of log k_{ex} values on p*D* under more acidic conditions. In addition, we observed that the *N*-pyridyl triazolium salt **13** displays a different *N*-aryl substituent effect to all other triazolium substrates. Formal acid catalysis of deuterium exchange was uniquely observed for *N*-pyridyltriazolium salt **13** under more acidic conditions, providing evidence for a possible intramolecular deprotonation reaction involving the pyridyl substituent.



EXPERIMENTAL

The syntheses of triazolium salts **11–14**, the preparation of solutions, the determination of p*D* and NMR methods are described in the Supporting Information.

Kinetic measurements

The kinetic procedures for the measurement of rate constants for deuterium exchange for triazolium salts **11–14** were identical to those previously reported for the study of analogous salts **6a–f**.[21] Because of the lability of the triazolium salts towards C(3)-H/D exchange in unbuffered D_2O solvent, reactions were initiated by addition of a solution, containing internal standard (tetramethylammonium deuteriosulfate) and buffer or DCl, directly to the rigorously dried triazolium salt. The final

substrate and internal standard concentrations in the D_2O reaction solutions were 5 and 1 mM, respectively. Reaction solutions in NMR tubes were incubated at 25 °C in a thermostated water bath. p*D* values were recorded at the beginning and end of each reaction and were found to be constant within error (±0.05). The progress of the C(3)-H/D deuterium exchange reaction was followed by ^{1}H-NMR spectroscopy during the disappearance of 75–90% of the C(3)-H signal of each substrate. There was no change in the integrated areas of signals of all other protons of triazolium salts **11–13** during this period, and no appearance of new signals, consistent with the absence of any parallel decomposition or hydrolysis reactions under the reaction conditions. For *N*-pyrimidinyl salt **14**, a competing reaction was observed to occur to a small extent accounting for ≤6% of total products. On the basis of the NMR signals of the products formed, this reaction was presumed to be a nucleophilic aromatic substitution reaction of DO^- or D_2O at C(2) of the pyrimidinyl ring.

The observed pseudo first order rate constants for exchange of the C(3)-proton for deuterium, k_{ex} (s^{-1}), were obtained from nonlinear least square fitting of reaction progress against time to a first order exponential decay function. Reaction progress was defined by values of *f* (s), the fraction of remaining unexchanged substrate, which were calculated from Eqn (1), where A_{C3H} and A_{std} are the integrated areas of the singlet of the C(3)-H of the triazolium salt and the broad triplet at 3.3 ppm because of the methyl hydrogens of internal standard, tetramethylammonium deuterosulfate. In the case of triazolium salt **14**, small corrections were made for the parallel S_NAr reaction of substrate such that the corrected *f* (s) values represented reaction because of deuterium exchange only.

$$f(s) = \frac{(A_{C_3H}/A_{std})_t}{(A_{C_3H}/A_{std})_0} \quad (1)$$

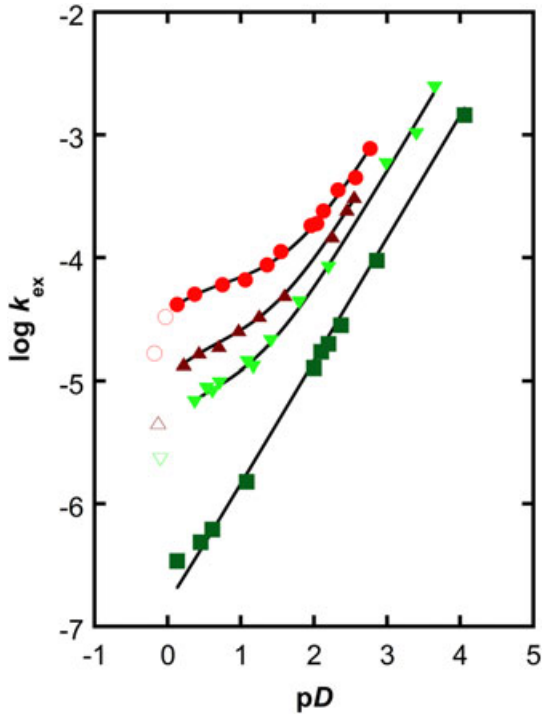


Figure 1. p*D* rate profiles for the deuterium exchange reactions of the C(3)-proton of triazolium salts **11** (▲) and **12** (▼) in D_2O at 25 °C and I = 1.0 (KCl). Also plotted for comparison are log k_{ex} – p*D* data taken from R. S. Massey *et al.*[21] for the deuterium exchange reactions of triazolium salts **6a** (●) and **6d** (■). The solid lines show the fits of the data at ionic strength, I = 1.0, to Eqn (3) except for **6d**[21] for which data are fit to an equation allowing for only a first order dependence on DO^-. For triazolium salt **11** and **12**, extra data points (△ and ▽) were obtained in 2 M DCl (shown as open symbols on the same profiles, as for **6a** additional data points[21] in 1.2 and 2 M DCl)

Representative NMR spectral overlays of the deuterium exchange reactions, first order kinetic plots, tabulated k_{ex} data and log k_{ex} – p*D* rate profiles are included in the Supporting Information for each triazolium salt **11–14** (Figs. S1–S16, Tables S1–S4).

RESULTS AND DISCUSSION

The C(3)-H/D deuterium exchange reactions of triazolium salts **11–14** were performed in aqueous acetic acid buffer or DCl solutions at a range of p*D* values and at constant ionic strength, I = 1.0 (KCl). For these substrates, deuterium exchange was too fast to monitor above p*D* 4 at 25 °C. Buffer catalysis of deuterium exchange was found to be insignificant in all previous studies of azolium ion conjugate acids of NHCs including representative triazolium salts.[18,20,21] Hence, it was assumed that buffer catalysis of exchange was not significant, and the observed pseudo first order rate constants for exchange, k_{ex} (s^{-1}), for reactions performed in acetic acid buffers were used directly on p*D* rate profiles of deuterium exchange.

As in the previous study of a large series of triazolium salts, values of log k_{ex} for **11** and **12** (Fig. 1, ▲ and ▼) increase with p*D* in the region from p*D* = 0–4.5. Figure 1 shows the p*D* rate profiles for these salts in comparison with those for two previously studied *N*-pentafluorophenyl and *N*-phenyl triazolium salts **6a** and **6d**, respectively. Figure 2 shows the p*D* rate profiles for *N*-pyridyl and *N*-pyrimidinyl salts **13** and **14** also in comparison with previous data for **6a** and **6d**, respectively. The data for *N*-pyridyl triazolium salt **13** (Fig. 2, ♦) is distinctly different from all other triazolium salts studied including *N*-pentafluorophenyl substrate **6a**. Values of log k_{ex} for **13** *decrease* with p*D* in the region

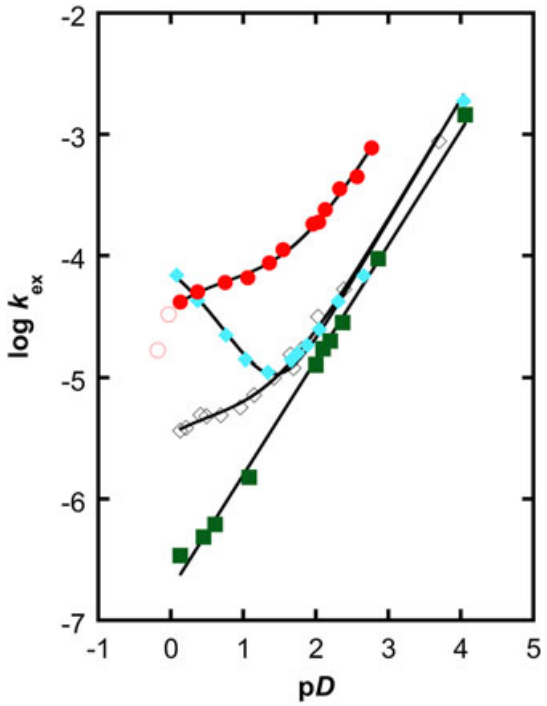


Figure 2. p*D* rate profiles for the deuterium exchange reactions of the C(3)-proton of triazolium salts **13** (♦) and **14** (◇) in D_2O at 25 °C and I = 1.0 (KCl). Also plotted for comparison are log k_{ex} – p*D* data taken from R. S. Massey *et al.*[21] for the deuterium exchange reactions of triazolium salts **6a** (●) and **6d** (■). The solid lines show the fits of the data to Eqn (3) for **6a** and **14** and Eqn (4) for **13**. For **6d**,[21] the data are fit to an equation allowing for only a first order dependence on DO^-

from p*D* = 0–1.3 and increase with p*D* in the region 1.3–4.5. By contrast, the log k_{ex} – p*D* profile for *N*-pyrimidinyl salt **14** (Fig. 2, ◇) is comparable with those for **11** and **12** displaying an increase of rate constants for exchange with p*D* in the whole region studied.

*Deuterium exchange reactions of N-2,4,6-tribromophenyl **11** and N-2,6-dichlorophenyl **12** triazolium tetrafluoroborates*

Deuterium exchange kinetic data for *N*-2,4,6-tribromophenyl- and *N*-2,6-dichlorophenyl triazolium salts **11** and **12** show the same dependencies on p*D* as observed for *N*-pentafluorophenyl salt **6a**. In particular, there is a marked change in the dependence of log k_{ex} values on p*D* under more acidic conditions closely similar to data for **6a** and more significant than for **6b–f**. At p*D*s >1.5, values of log k_{ex} for **11** and **12** increase linearly with p*D*, and the data may be fit by a line of unit slope indicating a first order dependence on deuteroxide ion concentration in this region. This is consistent with a mechanism involving deuteroxide-catalysed C3-H/D exchange of the monocationic triazolium ion substrate (path A, Scheme 1). At p*D*s <1.5, the dependencies of log k_{ex} on p*D* decrease, and data points in this region deviate upwards from the line of unit slope that fits the remaining data at higher p*D*s. There is also the beginning of a further downward break at the lowest p*D* values as observed previously for *N*-pentafluorophenyltriazolium salt **6a**. By comparison, the profile for unsubstituted *N*-phenyl salt **6d** (Fig. 2, ■) is essentially linear with slope unity for all data points except at p*D*s <0.2.

As in our previous study for **6a**, the data for salts **11** and **12** fit well to a kinetic scheme allowing for the occurrence of either path B or C at lower p*D*s in conjunction with path A at higher p*D*s. The log k_{ex} – p*D* data fits well to Eqn (2) *or* (3) that allow for paths A and B *or* paths A and C, respectively. In these equations, k_{DO} ($M^{-1}\,s^{-1}$) is the second order rate constant for deprotonation of monocationic triazolium ion (cf. **6**, Scheme 1) by deuteroxide, $K_w = 10^{-14.87}$ is the ion product of D_2O at 25 °C, $\gamma_{DO} = 0.73$ is the activity coefficient for deuteroxide ion under our experimental conditions, K_a^N is the acidity constant for ionization at N, k_{D2O} (s^{-1}) is the first order rate constant for deprotonation of monocationic triazolium ion at C(3) by solvent D_2O and k_{DO}' ($M^{-1}\,s^{-1}$) is the second order rate constant for deprotonation of dicationic triazolium ion (cf. **8**, Scheme 1) by deuteroxide ion. Fitting to either equation yields identical values for k_{DO} and K_a^N (Table 1), whereas values for k_{D2O} or k_{DO}' are obtained by fitting to Eqn (2) or (3), respectively (Table 2). For comparison, previously reported data[21] for *N*-pentafluorophenyl and phenyl salts **6a** and **6d** are also included in Tables 1 and 2.

$$\log k_{ex} = \log\left[\frac{K_a^N\left(\left(\frac{k_{DO}K_w}{\gamma_{DO}}\right)10^{pD}\right) + \left(K_a^N k_{D_2O}\right)}{K_a^N + 10^{-pD}}\right] \quad (2)$$

$$\log k_{ex} = \log\left[\frac{K_a^N\left(\left(\frac{k_{DO}K_w}{\gamma_{DO}}\right)10^{pD}\right) + \left(\frac{k'_{DO}K_w}{\gamma_{DO}}\right)}{\left(K_a^N + 10^{-pD}\right)}\right] \quad (3)$$

Values of the second order rate constants, k_{DO}, for C(3)-deprotonation by deuteroxide ion of triazolium salts **6a**, **6d**, **11** and **12** decrease in the order **6a** > **11** > **12** > **6d**, although the difference across this series is only 10-fold (Table 1). Similarly, small *N*-aryl substituent effects were observed for the 20 triazolium salts previously studied with k_{DO} values only varying by a maximum of 37-fold across this large series. The order of reactivity of triazolium salts corresponds to an increase in rate constant for deprotonation at C(3) with more electron withdrawing *N*-aryl substituents. The k_{DO} value for 2,4,6-tribromophenyl triazolium salt **11** is 2.6-fold higher than for 2,6-dichlorophenyl analogue **12**. Although a chloro substituent is more electron withdrawing than bromo, the greater number of halogen atoms in **11** results in a higher observed kinetic acidity towards deuteroxide ion.

The acidity constants for protonation at nitrogen, K_a^N, increase in the order **11** < **12** < **6a** and correspond to pK_a^N values of −0.04, −0.11 and −0.18, respectively (Table 1). The relatively large fitting errors associated with these K_a^N values are expected as only ~50% *N*-protonation has occurred at p*D* = 0. The values for pK_a^N are similar within error, and the data shows that there is a small increase in the degree of *N*-protonation within the normal pH range in the order **6a** < **12** < **11**. Importantly, as

Table 1. Second order rate constants for deuteroxide-catalysed hydrogen–deuterium exchange at C(3) (k_{DO}, $M^{-1}\,s^{-1}$), carbon acid pK_a^{C3} and pK_a^N values in aqueous solution at 25 °C and ionic strength, I = 1.0 (KCl)

Salt	k_{DO} ($M^{-1}\,s^{-1}$)[a]	pK_a^{C3}[c]	K_a^N (M)[d]	pK_a^N
11	$4.29\ (\pm0.13)\times10^{8}$[a]	16.7	1.1 (±0.3)	−0.04
12	$2.71\ (\pm0.12)\times10^{8}$[a]	16.9	1.3 (±1.3)	−0.11
13	$1.05\ (\pm0.05)\times10^{8}$[a]	17.3	0.9 (±0.4)	0.05
14	$1.07\ (\pm0.03)\times10^{8}$[a]	17.3	2.3 (±1.6)	−0.36
6a	$6.82\ (\pm0.25)\times10^{8}$[b]	16.5[b]	1.5 (±0.4)[b]	−0.18[b]
6d	$6.82\ (\pm0.13)\times10^{7}$[b]	17.5[b]	[e]	[e]

[a]Values of k_{DO} ($M^{-1}\,s^{-1}$) obtained by fitting log k_{ex} – p*D* data to Eqn (2) or (3).
[b]Taken from R. S. Massey *et al.*[21]
[c]pK_a^{C3} values obtained by application of Eqn (5).
[d]Values of K_a^N (M) obtained by fitting log k_{ex} – p*D* data to Eqn (2) or (3).
[e]Value could not be determined because of limited data points showing an altered dependence on p*D* as described in the main text.

Table 2. Predicted rate constants for k_{D2O}, k_{DO}' or k' based on kinetic fitting

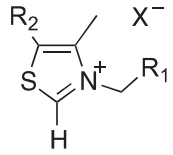
Salt	k_{D2O} (s^{-1})[a]	k_{DO}' ($M^{-1}\,s^{-1}$)[d]
11	2.0×10^{-5} ($\pm3.8\times10^{-6}$)	1.2×10^{10} ($\pm2.2\times10^{9}$)
12	8.0×10^{-6} ($\pm6.6\times10^{-6}$)	5.7×10^{9} ($\pm4.7\times10^{9}$)
14	4.7×10^{-6} ($\pm2.6\times10^{-6}$)	5.9×10^{9} ($\pm3.3\times10^{9}$)
6a	6.1×10^{-5} ($\pm3.6\times10^{-7}$)[b]	3.3×10^{10} ($\pm2.0\times10^{9}$)[b]
13	1.4×10^{-4} ($\pm4.3\times10^{-5}$)[c]	

[a]Values of k_{D2O} (s^{-1}) obtained by fitting log k_{ex} – p*D* data to Eqn (2).
[b]Taken from R. S. Massey *et al.*[21]
[c]Value of k' (s^{-1}) obtained by fitting log k_{ex} – p*D* data to Eqn (4).
[d]Values of k_{DO}' ($M^{-1}\,s^{-1}$) obtained by fitting log k_{ex} – p*D* data to Eqn (3).

observed previously for **6a**, the pK_a^N values for **11** and **12** must be substantially higher than for *N*-phenyl salt **6d** (Fig. 2) and other N-aryl salts **6b–f**. The p*D* profiles for **6b–f** are linear through most of the p*D* region studied, with only one to three data points at the lowest p*D*s showing upward deviation; thus, pK_a^N values for **6b–f** could not be obtained. It can be presumed that the pK_a^N values are significantly less than zero for **6b–f** with no substantial protonation at N1 in the normal p*D* range.

Notably, the profiles for *N*-4-cyanophenyl **6b** and 2,6-dichlorophenyl **12** substrates are almost superimposable at p*D*s >1.5 yielding similar k_{DO} values (Fig. S17); however, the altered dependence on p*D* is greater for **12** under more acidic conditions. As the electronic substituent effect on k_{DO} is similar in both cases, this supports the existence of an additional *ortho*-chloro substituent effect to explain the observed differences in pK_a^N. This *N*-aryl net *donor* effect on pK_a^N for **6a**, **11** and **12** is opposite to the normal inductive through-bond electron accepting substituent effect of these substituents, which would favour an increase in acidity. Instead, we observe an increase in the basicity of N(1) for **6a**, **11** and **12** relative to other *N*-aryl triazolium ions **6b–f**. The only possible explanation of these substituent effects on pK_a^N lies in through-space interactions as proposed earlier, as otherwise a normal inductive substituent effect would be expected as observed on acidity at C(3). Although the pK_a^N values for **6a**, **11** and **12** are similar within error, the highest observed value is for triazolium salt **11** with the largest *ortho*-bromo substituents, and it is possible to speculate that this facilitates a donor interaction with N(1).

Previously,[21] we suggested that path C rather than B was the most likely mechanism under more acidic conditions to explain the altered dependence of log k_{ex} values on p*D*. This was mainly based on a comparison of rate constants for deuterium exchange for triazolium ion **6a** with analogous literature data for thiazolium ions **15**.[23,25] There is no additional site for protonation within the thiazolium ring of **15** unlike for the triazolium analogue **6a**. Washabaugh and Jencks did observe the onset of a true p*D*-independent solvent reaction for four thiazolium salts **15** in concentrated DCl solutions at p*D*s $<<0$ yielding rate constants, k_{D2O}, that range from $1.6\times10^{-9}\,s^{-1}$ up to $9.4\times10^{-8}\,s^{-1}$. In a comparison of data for triazolium and thiazolium salts, we previously noted that the difference in k_{DO} values is significantly smaller than for k_{D2O} values. As an example, $k_{DO}=4.67\times10^{7}\,M^{-1}\,s^{-1}$ for the *N*-cyanomethyl thiazolium salt **15** ($R_1=CN$, $R_2=H$), which is 14-fold lower than $k_{DO}=6.82\times10^{8}\,M^{-1}\,s^{-1}$ for *N*-pentafluorophenyltriazolium salt **6a** (Table 1), whereas there is a much greater 650-fold difference for the corresponding k_{D2O} values [$k_{D2O}=9.4\times10^{-8}\,s^{-1}$ for **15** ($R_1=CN$, $R_2=H$) versus $k_{D2O}=6.1\times10^{-5}\,s^{-1}$ for **6a** (Table 2)]. It is difficult to explain a substantially larger ring effect on the solvent compared with the deuteroxide-catalysed deuterium exchange reactions, and we suggested that this provides evidence that path B is not the correct mechanism to account for our data at low p*D*s. Further, the *N*-protonated dicationic substrate would be expected to be more acidic at C(3) than the monocationic analogue, and it seems logical (because of the requirement for *N*-protonation to explain the observed log k_{ex} – p*D* data for **6a**) that a deuteroxide reaction of the dication would be more likely than a water reaction on the monocation given the greater reactivity of *both* the substrate and the base in the former case, albeit at very low concentrations of DO^-.



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The new data in Table 2 for triazolium salts **11** and **12** supports these conclusions. The k_{D2O} values calculated for **11** and **12** using Eqn (2) are 85-fold to 213-fold larger than observed for the true p*D*-independent solvent reactions of the *N*-cyanomethyl thiazolium salt **15** ($R_1=CN$, $R_2=H$), whereas there is a much smaller ring effect on k_{DO} values (<10-fold), again suggesting that path B does not occur for the former triazolium ions. Estimates for k_{DO}' calculated for C(3)-deprotonation of the dicationic conjugate acids of **11** and **12** (cf. **8** in Scheme 2), for reaction *via* path C, are all at the diffusional limit (Table 2). This is logical given that k_{DO} values for the less reactive monocationic salts are already as high as $\sim10^{8}\,M^{-1}\,s^{-1}$. Further, as will be seen in the succeeding texts, the observed acid catalysis in the case of *N*-pyridyl salt **13** is most logically accounted for in tandem with path C for the other triazolium salts at lower p*D*s.

*Deuterium exchange reactions of N-pyridyltriazolium **13** and N-2,6-pyrimidinyl **14** triazolium tetrafluoroborates*

As for triazolium salts **11–12**, values of log k_{ex} for *N*-pyridyl salt **13** increase linearly at p*D*s >1.5 (Fig. 2, ♦), and the data may be fit by a line of unit slope consistent with a first order dependence on deuteroxide ion concentration in this region and deuterium exchange *via* path A (Scheme 1). In contrast with data for the other triazolium salts in Fig. 1, values of log k_{ex} for **13** *decrease* with p*D* in the region from p*D* = 0–1.3. This observed acid catalysis of deuterium exchange requires protonation of substrate and a *subsequent* p*D*-independent C(3)-deprotonation of the resulting dicationic substrate.

The log k_{ex} – p*D* data for *N*-pyridyl salt **13** fits well to Eqn (4), which allows for both deuteroxide-catalysed exchange on the monocationic triazolium salt (path A, Scheme 1) and, additionally, a p*D*-independent C(3)-deprotonation reaction on the dicationic substrate. In Eqn (4), k_{DO}, K_w and γ_{DO} are as defined earlier in the text. The first order rate constant k' (s^{-1}) refers to p*D*-independent deprotonation of dicationic substrate, and mechanistic options for this process are discussed in the succeeding texts. In this case, either the pyridyl nitrogen or N1 of the triazolium ring could potentially be protonated to give a dicationic species. The $pK_a^N=0.05$ calculated for *N*-pyridyl substrate **13** (Table 1) is similar to pK_a^N values for triazolium salts **6a**, **11** and **12** for which additional protonation can only occur at N(1) of the triazolium ring. However, $pK_a^N=0.05$ may also be consistent with the acidity constant for the pyridinium nitrogen. Numerous solution studies establish the pK_a of the *N*-protonated pyridinium ion at ~5,[26] and this would be expected to substantially decrease in the presence of a monocationic triazolium substituent.

$$\log k_{ex} = \log\left[\frac{K_a^N\left(\left(\frac{k_{DO}K_w}{\gamma_{DO}}\right)10^{pD}\right)+k'\left(10^{-pD}\right)}{K_a^N+10^{-pD}}\right] \qquad (4)$$

Possible mechanisms formally consistent with the observed acid catalysis of deuterium exchange for *N*-pyridyl salt **13** at lower p*D*s are shown in Scheme 3. In analysing these options, a key consideration is whether these mechanisms can explain why a p*D*-independent reaction of the *N*-protonated salt is possible for **13** but has not been observed for any other triazolium ion. Option D1 (Scheme 3) involves initial protonation on N1 of the triazolium ring followed by p*D*-independent deprotonation by D_2O *without* direct involvement of the pyridyl ring. This mechanism may be discounted as acid catalysis of deuterium exchange has not been observed for any other triazolium ion studied to date, and a remote pyridyl substituent would not be expected to drastically increase the rate of deprotonation of dicationic substrate by solvent, especially as k_{DO} values for exchange *via* path A (Scheme 1) are similar for **13** and other triazolium salts studied.

Option D2 (Scheme 3) involves initial protonation on the pyridyl nitrogen, rather than N1 of the triazolium ring, followed by p*D*-independent deprotonation by water. Remote protonation on the adjacent pyridyl ring would not significantly increase the rate of deprotonation at C(3) by solvent to enable competition with path C (Scheme 1). The latter would be expected to be faster because of N1-protonation on the more proximal triazole ring with subsequent C(3) deprotonation by more basic deuteroxide ion. *N*-Protonation of the pyridyl substituent could, in theory, increase the rate of deprotonation by water at C(3) to compete with a water reaction of the monocationic triazolium salt (path B, Scheme 1). However, the data for all other triazolium salts requires protonation at N1, as the p*D* rate profiles do not show p*D*-independence and log k_{ex} values continue to decrease; hence, this latter option is self-contradictory. Protonation of the more proximal triazolium ring should then also result in a competing water reaction such as D1, and acid catalysis would also be expected for the other triazolium salts. On this basis, option D2 cannot account for the unique observation of acid catalysis for **13** in competition with either path B or C for the other triazolium salts.

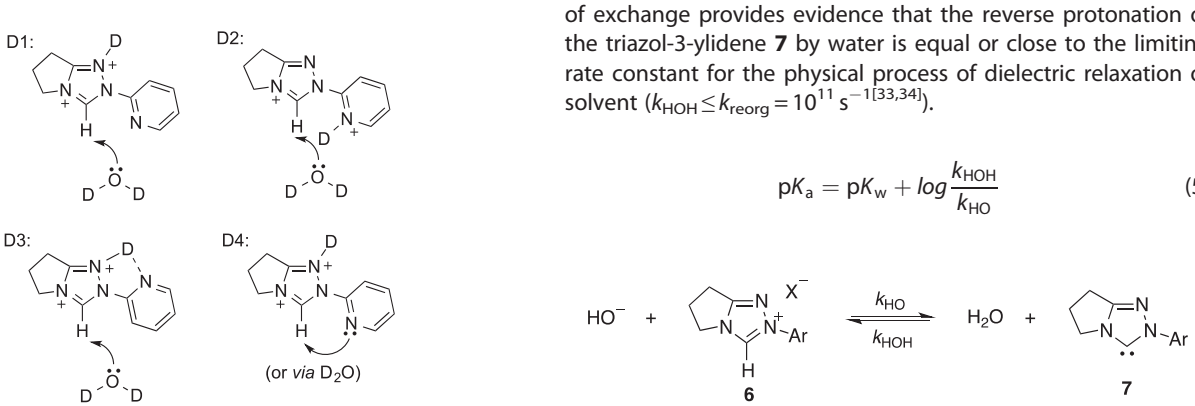
Another possibility is that a shared hydrogen bond forms between N1 on the triazole and the pyridyl nitrogen thereby accelerating the rate of deprotonation at C(3) by solvent (option D3, Scheme 3). However, the geometry of this hydrogen bond is not linear, and it is difficult to envisage why this would occur only for a solvent deprotonation reaction and not for deprotonation by deuteroxide ion. A final option (D4, Scheme 3) is compatible with the occurrence of acid catalysis in the case of the *N*-pyridyl salt only and also supports path C as the main mechanism for deuterium exchange at lower p*D*s for the other triazolium salts **6a**, **11** and **12** rather than path B. In this mechanism, observed acid catalysis can be explained by *N*-protonation on the triazolium ring accompanied by intramolecular deprotonation at C(3) by the pyridyl nitrogen. This intramolecular deprotonation could be direct or may involve one or more solvent molecules. As this option is not available to the other substrates **6a**, **11** and **12**, it could provide an explanation for the singular occurrence of acid catalysis in the case of *N*-pyridyl substrate **13** only.

The log k_{ex} – p*D* profile for *N*-pyrimidinyl salt **14** (Fig. 2, ◇) is comparable with those for **11** and **12** displaying an increase of rate constants for exchange with p*D* in the whole region studied, and no acid catalysis of deuterium exchange is observed at lower p*D*s. This suggests that intramolecular catalysis, through C(3) deprotonation by the adjacent pyrimidine ring, is not significant in this case. Given the much decreased basicity of a simple monocyclic pyrimidine relative to a pyridine nitrogen (pK_as of 5.1 and 1.1 for *N*-protonated pyridinium and pyrimidinium ions, respectively),[26] this is likely because intramolecular deprotonation by the less basic pyrimidine nitrogen cannot compete with intermolecular deprotonation at C(3) by deuteroxide ion under these conditions. The data for *N*-pyrimidinyl salt **14** fits well to Eqn (2) or (3), and the resulting values for k_{DO}, K_a^N and k_{D2O} or k_{DO}' are shown in Tables 1 and 2. Significantly, the observed p$K_a^N = -0.36$ for the *N*-pyrimidinyl substrate **14** is very similar to that observed for *N*-pyridyl substrate **13** (p$K_a^N = 0.05$) and provides further evidence that protonation occurs on the triazolium N(1) rather than the pyrimidine ring, which would be expected to yield more different pK_as. This lends further support to reaction *via* path C as the dominant mechanism for all salts, except *N*-pyridyl triazolium ion **13**, at lower p*D*s.

Estimation of carbon acid pK_a values

The carbon acid pK_a values for deprotonation at C(3) for monocationic triazolium salts **11–14** may be determined using Eqn (5), which is derived for Scheme 4.[18,20–22,27–31] In this equation, k_{HO} ($M^{-1}\,s^{-1}$) is the second order rate constant for deprotonation at C(3) by hydroxide ion, which may be calculated from the corresponding k_{DO} value using a value of $k_{HO}/k_{DO} = 2.4$[32] for the secondary solvent isotope effect on the basicity of HO^- in H_2O versus DO^- in D_2O. As discussed previously,[18,20,21] the absence of significant general base catalysis of exchange provides evidence that the reverse protonation of the triazol-3-ylidene **7** by water is equal or close to the limiting rate constant for the physical process of dielectric relaxation of solvent ($k_{HOH} \leq k_{reorg} = 10^{11}\,s^{-1}$[33,34]).

$$pK_a = pK_w + log\frac{k_{HOH}}{k_{HO}} \qquad (5)$$



Scheme 3. Potential mechanistic options for p*D*-independent deprotonation of a dicationic *N*-deuteronated *N*-pyridyl triazolium salt

Scheme 4. Equilibrium for deprotonation by hydroxide of triazolium ions **6** at C(3)

The C(3)-H pK_a values for triazolium salts **11–14** are similar and range from 16.7 to 17.3. The values are comparable with those estimated for related thiazolium ions (cf. **15**), however, are substantially lower than our previously published values for the conjugate acids of imidazole-2-ylidenes **2**, imidazolin-2-ylidenes **3** and trihydropyrimidin-2-ylidenes. This is due to the presence of the additional electron withdrawing ring nitrogen, which increases the stability of the formally neutral NHC **7** relatively to the cationic conjugate acid **6**. This large in-plane electron withdrawing effect of nitrogen is relatively common in heterocyclic systems. As mentioned earlier, the pK_a of *N*-protonated pyrimidine is four units lower than for the pyridinium ion because of the additional ring nitrogen atom in the former system.

The estimated k_{DO}' values for C(3)-deprotonation of *N*-protonated **6a**, **11**, **12** and **14** by deuteroxide ion (Table 2) are at the diffusional limit. The new k_{DO}' data for **11**, **12** and **14** are all safely within error of typical bimolecular values for diffusion of small molecules in solution ($k_d \sim 5 \times 10^9\ M^{-1}\ s^{-1}$). This provides confidence in a stepwise rather than concerted mechanism for deuterium exchange at C(3) of the dicationic salt, *via* a distinct monocationic NHC intermediate, as shown in Scheme 1 (path C). To our knowledge, a monocationic NHC **9**, or a N1-alkylated analogue, has not been directly isolated to date, and these additional results for **11**, **12** and **14** provide evidence for the transient formation of these species in aqueous solution under acidic conditions.

The C(3)-carbon acid pK_a values for N(1)-protonated dicationic triazolium salts (cf. **8**, Scheme 1) would be predicted to be substantially lower than for monocationic triazolium ions **6**. By analogy with the first and second pK_a^Ns for simple diprotonated and monoprotonated nitrogen-containing heterocycles, the decrease in pK_a would be expected to be at least five units. It is predicted that the reverse protonation of the monocationic NHCs (cf. **9**) will fall below the upper limiting rate constant for protonation by solvent ($k_{reorg} = 10^{11}\ s^{-1}$). Using an average value of $k_{DO}' = 5 \times 10^9\ M^{-1}\ s^{-1}$ together with $k_{HOH} \leq 10^{11}\ s^{-1}$ in Eqn (5) yields an upper limit estimate of p$K_a \leq 15.3$ for the C(3)-carbon acidity of a dicationic triazolium ions. These pK_as establish the conjugate acids **8** of monocationic carbenes **9** as the most acidic of all NHC families studied to date in aqueous solution.

CONCLUSIONS

Our studies of the deuterium exchange reactions of *ortho*-disubstituted triazolium salts **11–12** provide additional evidence for formal 2-heteroatom donor effects on pK_a values at N(1). In particular, there is a marked change in the dependence of log k_{ex} values on p*D* under more acidic conditions closely similar to data for **6a** and more significant than for **6b–f** where the latter have only hydrogens or methyl groups rather than halogens in the 2-position. Although the p*D* profiles for all the triazolium ions **6a–f** and **11–12** are very similar above p*D* 1.5 yielding k_{DO} values within ~10-fold of each other, the altered dependence on p*D* under more acidic conditions is more dominant for 2-halo-substituted ions **6a**, **11** and **12** than for **6b–f**. The calculated pK_a^N values decrease in the order Br > Cl > F, although the difference is small across the series. The donor effect on pK_a^N, which favours protonation at N(1), may be to suppress unfavourable electrostatic interactions between N(1) and spacially proximal *N*-aryl *ortho*-heteroatoms or could be a result of stabilizing through-space N^+-H…*ortho*-X interactions in the *N*-protonated salt.

The present study also reveals unique substituent effects for the *N*-(2-pyridyl)-triazolium system **13**, which shows distinct acid catalysis of deuterium exchange at lower p*D* values. We propose that this data is best explained by invoking an intramolecular general base role for the *N*-(2-pyridyl) substituent in conjunction with N1-protonation on the triazolium ring. Future work will investigate the effect of additional substitution by both donor and acceptor groups on the 2-pyridyl *N*-aryl ring, as a means of further exploring the proposed intramolecular proton transfer reaction. In addition, the potential of *ortho*-amino groups of *N*-2-anilino substituents will be probed as alternative intramolecular general base catalysts.

Overall, these results highlight the varying roles of *ortho*-heteroatoms in influencing the chemical behaviour of widely used triazolium salts in organic catalysis.

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